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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,946	04/19/2001	L. David Williams	MVIEWD.1A2DV1	5256

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EXAMINER
SAIDHA, TEKCHAND

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,946	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE f this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *42-76* is/are pending in the application.

4a) Of the above claim(s) *42-49 and 60-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *50-59 and 74-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election

1. Applicant's election with traverse of Group II (claims 50-59 & 74-76) in Paper No. 22 (filed 07.10.03) is acknowledged. The traversal is on the ground(s) that patentability of the uricases lies in the fact that, regardless of their species of origin, the uricases all contain the tetrameric form of uricase and are substantially free of uricase aggregates. This is not found persuasive because Applicants claims are drawn to a multitude of uricase products and from a variety of species, wherein each of the species (or uricases) originating from a different source (mammal or microbial, plant, etc) not only have varying level of uricase activity but a distinct structure as evidenced by their known amino acid sequences [Chen et al. (1981) and references therein], but also require a distinct purification scheme for purifying the uricase from the source in question. Applicants have exemplified a single purification scheme purifying the tetrameric form of porcine liver uricase by size exclusion chromatography (see Example I, pages 19-20 of the instant specification). However, and as is well known in the protein purification art there is no single procedure for purifying an enzyme or protein from a variety of sources using a single method. This is substantiated by the diverse physical and chemical properties exhibited by uricases from different sources (see for example, Chen et al. BBA 660 : (1981) : 293-298). Chen et al. describe properties of Hog liver & *Candida utilis* urate oxidase or uricase having different physical and chemical properties. Chen et al. further, examined preparation of Hog liver (US Biochemical Corp., Catalog No. 23095) uricase to be 93% pure and *C. utilis* uricase [Toyobo Co. Ltd., Osaka, Japan] to be highly pure showing a single band on gel-electrophoresis. Thus, each of the uricases are patentably distinct products as explained above. Therefore the restriction

of claims to separate groups is proper and is maintained. Applicants further argue that the groups III-VI are classified in the same class. In response, it is stated that even though they are classified in the same class/subclass, additional subclasses have to be searched. For example – DNA encoding an animal polypeptide require searching for class 536, subclass 23.5; DNA encoding plant polypeptide require searching for class 536, subclass 23.6; DNA encoding microbial polypeptide require searching for class 536, subclass 23.7, apart from searching for 435/191. This additional searching as explained above would therefore involve undue burden to the Examiner. The requirement is still deemed proper and is therefore made FINAL.

2. Claims 50-59 & 74-76 are pending and under consideration in this examination.

3. Claims 42-49 & 60-73 are withdrawn from consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 22.

4. ***Continuation of prior application***

When a non-provisional application is converted to a provisional application, the serial number of the *converted* non-provisional application should *not* be listed in the continuing data. For example:

A non-provisional application 08/XXX,XXX, filed 6/20/97, is converted to a provisional application 60/YYY,YYY (*which keeps the 6/20/97 filing date*). A non-provisional application 08/ZZZ,ZZZ is filed 6/15/98 claiming the benefit of the provisional application 60/YYY,YYY. In this example, the first sentence of the specification of 08/ZZZ,ZZZ should read "This application claims the benefit of U.S. Provisional Application No. 60/YYY,YYY, filed 6/20/97."

The continuing data section on the jacket should read "PROVISIONAL APPLICATION NO. 60/YYY,YYY 06/20/97".

Correction is required.

5. ***Specification***

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

6. Claims 74-76 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a purified porcine uricase .

Factors to be considered in determining whether undue experimentation is required, are summarized in *re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) [*Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

It is neither taught nor any data is provided for using the uricase in pharmaceutical compositions for the treatment of any of the diseases or disorders. There is no evidence presented that uricase is associated with any of the known diseases or disorders or can be treated by administering the uricase. Without such a data or evidence, claims to pharmaceutical composition comprising uricase, would amount to a composition or potential drug for treatment for any disorder or disease, which is not enabled. Given the lack of direction or guidance and the nature of the invention, obtaining such a composition for one of skill in the art would be highly unpredictable. This is because the polypeptide when associated with a particular disease or disorder would be expressed differentially. Manipulating or controlling these levels depends

upon the disease or disorder, and may not always be controlled by supplementing with such a polypeptide composition. Further, no guidance in provided, pertaining to the fate of the administrated polypeptide in vivo.

Since it is not routine in the art to engage in *de novo* experimentation to prepare numerous compositions where the expectation "of success is unpredictable", the skilled artisan would require additional guidance, specific to individual disorder or disease, in order to make and use pharmaceutical compositions in a manner reasonably commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

7. ***Enablement***

Claims 50-59 & 74-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for uricases porcine, baboon, or Chimeric or fusion pig-baboon (fusion of amino acid 1-225 of SEQ ID NO : 1 and amino acids 226-304 of SEQ ID NO : 2 ; or fusion of amino acid 1-288 of SEQ ID NO : 1 and amino acids 289-304 of SEQ ID NO : 2), does not reasonably provide enablement for any mammalian uricase - modified, fusion, chimeric, or truncated from any source. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988))[*Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the

predictability or unpredictability of the art, and (h) the breadth of the claim. The factors most relevant to this rejection are the scope of the claims, unpredictability in the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

The claims are drawn to encompass diverse mammalian uricases (claims 50-53) - modified, fusion, chimeric from any source. The specification, however, only disclose selected uricases discussed above. It is also well known that humans and certain primates do not possess the uricase enzyme [Chen et al. Science 239, 1288-1291 (1988), IDS **AT14**]. There is no disclosure or description of the numerous uricases from the various sources claimed; or the DNA encoding the enzyme from the various sources, as well as the chimeric (claims 54-56) modifications [A chimeric protein by definition is a fused protein in which 2 linked proteins are derived from two different organisms. (Source : Dictionary of Biochemistry and Molecular Biology, page 78, 2nd edition, J. Stenesh, A Wiley-Interscience Publication)] that can be performed in creating the vast array of variants. Despite knowledge in the art for the modification of proteins and while it is known that many chimeric protein construction are generally possible in any given protein it is impossible to determine which portions of the 2 proteins are so fused in order to generate the chimeric protein with a reasonable expectation of success. Certain regions in the sequence are critical to the protein's structure/function relationship, e.g. such as the regions directly involved in binding, catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These or other regions may also be critical determinants of antigenicity. Similarly specific mutational modifications at 97, 291 or 301 (claims 57-59) claimed without sequence identifier number and/or which portion of the chimera being modified, will result in undue experimentation in

order to determine which the mammalian uricase or chimeric sequences, known or those not known to date which may not have the same residue as that being replaced. For example, rat liver uricase has only 289 amino acid, therefore there are no amino acid residues at positions 291 or 301 [see Motojima et al. JBC 263 (32) : 16677-16681 (1988)].

Pharmaceutical composition claims (claims 74-76) have shown no demonstrated or art-recognized *in vivo* method of treatment to be enabled. A mere disclosure by the applicant listing speculative or possible uses for the compound in the composition is not considered to be supportive of enablement. Incidentally, the disclosure of a method of administering the composition to an animal for the purpose of obtaining antibodies is not considered to be showing of a method of treatment, on the basis that the composition used would be a composition and not a pharmaceutical composition. Since it is not routine in the art to engage in *de novo* experimentation to make conjugated uricases or compositions from such a diverse pool of organisms as well as obtain modifications of the uricases where the expectation "of success is unpredictable", the skilled artisan would require additional guidance in order to make and use the uricases in a manner reasonably commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

8. **Written description**

Claims 50-59 & 74-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 50-59 & 74-76 are directed to encompass diverse uricases (claims 50-53) - modified, fusion or chimeric (claims 54-59) from any mammal and composition thereof (claims 74-76. Claims 50-59 & 74-76 are rejected under this section of 35 U.S.C. 112 because the claims are directed to a genus of modified uricases including fused or chimeric or mutated (for

example, T301S) for which no structure is apparent. No description has been provided of the numerous uricases obtainable from numerous mammals, some lacking the activity –as explained above, and modification performed in order to obtain the modified uricase sequences encompassed by the claim. Claims to specific mutation without reference to a SEQ ID NO. lacks description. For example, when amino acid position '301' is modified in a uricase from porcine, the same positional modification may have no meaning in a sequence from baboon or human. Even the amino acid residue from different uricase species may have a different residue at position '301'. For example, rat liver uricase has only 289 amino acid, therefore there are no amino acid residues at positions 291 or 301 [see Motojima et al. JBC 263 (32) : 16677-16681 (1988)]. This situation is further aggravated when a chimeric or truncated (claim 59) protein(s) without structural details be modified at that position. No information, beyond the characterization of Uricases from *Aspergillus favus* and Soybean *Candida*, porcine, baboon, mouse [all known in the prior art], and fusion pig-baboon (fusion of amino acid 1-225 of SEQ ID NO : 1 and amino acids 226-304 of SEQ ID NO : 2 ; or fusion of amino acid 1-288 of SEQ ID NO : 1 and amino acids 289-304 of SEQ ID NO : 2) [not known in the prior art], have been provided by applicants which would indicate that they had possession of the claimed genus of modified uricases or compositions comprising the uricases from any mammalian source. The specification does not contain any disclosure of the structure of all the polypeptide sequences of the diverse uricases - modified, fusion, chimeric or variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including uricases which can have a wide variety of structures and functions which is not apparent from the disclosure. The specification discloses only a selected number of species of the claimed genus which is

insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

9. ***Claim Rejections - 35 U.S.C. § 112*** (second paragraph)

Claims 50-59 & 74-76 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 50, line 3 & claim 53, line recites 'substantially free of uricase aggregates'. It is not clear 'what a meant by 'substantially free' or 'uricase aggregates' (claim 50), and the specification does not define the phrase(s) or provide a measure of the expression. Further, it is unclear what is the % of purity of the uricase ? Claim 53, line 2, recites 'substantially the sequence of porcine,...'. It is not clear what portions of the uricase sequence is from which species. Therefore without a clear definition of the phrase(s), the claim is indefinite.

Deleting the phrase(s) 'substantially free' & 'uricase aggregates' or 'substantially' is suggested to overcome this rejection.

Claims 51-59 & 74-76 are included in the rejection for failing to correct the defect present in the base claim.

10. Claims 57-58 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 57-58 recite mutational modifications of specific amino acid residues without any reference to the sequence identifier number. The claims are indefinite because of lack of actual

SEQ ID Nos., which being the missing reference point, the specific mutational modifications have no meaning, are ambiguous and indefinite.

11. ***Claim Rejections - 35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 50-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. [B.B.A. 660, (1981) 293-298, IDS-**AS11**]. Chen et al. teach properties of two urate oxidases (Uricases), viz., *Candida utilis* and Hog (porcine). The claims are written so broadly as to be anticipated by the reference.

12. Claims 50-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. [Science 239, 1288-1291 (1988), IDS **AT14**]. Chen et al. teach the recombinant production of full length amino acid sequence of porcine Urate oxidase (uricase) which is tetrameric and is substantially pure or free of uricase aggregates, and therefore anticipates the claims.

13. Claims 50-53 are rejected under 35 U.S.C. 102(b) as being anticipated by any of the following sigma compounds : Sigma Catalog (1993), page no. 1002, Product Nos. U 3250, 292-8, U3500, U 9375 or U 3377. [Microbial uricases are also listed on the same page, not used as art]. Pure Urate oxidases (uricases) listed inherently are tetrameric and is substantially pure or free of uricase aggregates, and therefore anticipates the claims.

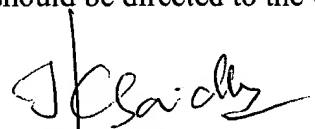
14. Claims 50-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al. [PNAS, USA, Vol. 86, pp. 9412-9416, December 1989]. Wu et al. teach the recombinant production and sequenced the urate oxidase or uricase from baboon, mouse and pig (porcine). The sequences are as pure as any protein can get and being free of aggregates anticipates the claims.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Tekchand Saidha
Primary Examiner, Art Unit 1652
September 9, 2003